Method for Synthesizing 5β, 6β-Epoxides of Steroids by a Highly β-Selective Epoxidation of Δ^5-Unsaturated Steroids Catalyzed by Ketones

[0001] This application is a continuation-in-part of non-provisional application Serial No. 09/788,201 filed February 16, 2001, which claims the benefit under 35 U.S.C. 119(e) of United States Provisional Application Serial No. 60/183,396 filed February 18, 2000.

Technical Field

[0002] The present invention is directed to the field of synthesizing epoxides of steroids.

Background of the Invention

[0003] Steroid epoxides are an important class of oxysterols (oxygenated derivatives of cholesterol) involved in the regulation of cell proliferation and cholesterol homeostasis. They are versatile intermediates for steroid synthesis and useful probes for biochemical studies of enzymes. Steroid epoxides are also useful intermediates for the preparation of other oxysterols. For example, α- and β-epoxides of cholesterol are auto-oxidation products of cholesterol *in vivo,* and both are cytotoxic and mutagenic. The isomeric α- and β-epoxides are hydrolysed by cholesterol 5,6-epoxide hydrolase to cholestane-3β,5α,6β-triol which has potent hypocholesterolemic activity. On the other hand, both epoxides inhibit the cholesterol 7α-hydroxylase which catalyzes the rate-determining step of bile acid synthesis. As 5α,6α-epoxides are readily available via epoxidation of Δ^5-unsaturated steroids with peracids, there have been extensive studies on the biological actions of those epoxides and their derivatives. In contrast, much less is known about the 5β,6β-epoxides and their derivatives because they are difficult to

obtain in high selectivity. More importantly, the 5β,6β-epoxy functionality is found in a number of naturally occurring steroids of antitumor activities, e.g., jaborosalactone A, withaferin A, and withanolide D.

[0007] Common organic oxidants such as 3-chloroperoxybenzoic acid (*m*CPBA) generally give α-epoxides as the major products for epoxidation of 3β-substituted Δ^5-steroids and show poor selectivities for epoxidation of 3α-substituted Δ^5-steroids except *epi*-cholesterol. This is because peracid epoxidation follows a concerted pathway via spiro transition states (α-TS and β-TS (TS = transition state); see Fig. 1). The β-TS suffers from steric interactions between the peracid and the C(10) angular methyl group for epoxidation of 3β-substituted Δ^5-steroids, while both the β-TS and the α-TS encounter similar steric hindrance for epoxidation of 3α-substituted Δ^5-steroids. Dioxiranes are new-generation reagents for oxidation under mild and neutral conditions. Unfortunately, poor selectivities were reported in epoxidation of 3β-substituted Δ^5-steroids by either isolated or in situ generated dioxiranes. While dioxiranes also epoxidize olefins through a spiro TS, their steric environment is different from that of peracids. To minimize steric interactions, dioxiranes prefer to approach the C(5)=C(6) double bond of Δ^5-steroids from the less-substituted side, i.e., away from the C(10)-angular methyl group and the C-ring of steroids (Fig. 1). Therefore, it is the potential steric interactions between the α-substituents of dioxiranes and the 3α and 4β substituents of steroids that determine the facial selectivity of epoxidation.

[0005] Yang et al., in U.S. 5,763,623 and in J. Org. Chem., 1998, vol. 63 pages 8952-8956, disclose the epoxidation of unfunctionalized olefins using various ketones. These references do not teach or suggest the epoxidation of Δ^5-unsaturated steroids.

[0006] Cicala, G., et al., J. Org. Chem., 1982, vol. 47, pages 2670-2673, disclose the epoxidation of a Δ^5-unsaturated steroid that is not a 3α-substituted Δ^5-unsaturated steroid, and in which the ketone catalyst is acetone.

[0007] Marples, B.A., et al. Tetrahedron Lett., 1991, vol. 32, pages 533-536, disclose the epoxidation reactions of four Δ^5-unsaturated steroids that are not 3α-substituted Δ^5-unsaturated steroids, and using a variety of ketones. In these reactions either no epoxide was observed, or the β/α-epoxide ratio was about 1:1.

[0008] Bovicelli, P., et al., J. Org. Chem., 1992, vol. 57, pages 2182-2184, disclose the epoxidation of a Δ^5-unsaturated steroid that is not a 3α-substituted Δ^5-unsaturated steroid, and using dimethyldioxirane. The β/α-epoxide ratio was about 3:1.

[0009] Boehlow, T.R., et al., Tetrahedron Lett., 1998, vol. 39, pages 1839-1842, disclose the epoxidation of a Δ^5-unsaturated steroid that is not a 3α-substituted Δ^5-unsaturated steroid, and using a variety of ketone catalysts.

[0010] Shi, Y., in PCT Publication No. WO 01/12616 A1, February 22, 2001, discloses an epoxidation method combining an olefin substrate, a ketone catalyst, a nitrile compound, and hydrogen peroxide.

[0011] Shi, Y., in PCT Publication No. WO 98/15544, April 16, 1998, discloses the use of a chiral ketal and an oxidizing agent with an olefin to generate an epoxide with high enantioselectricity.

SUMMARY OF THE INVENTION

[0012] In accordance with the invention, a method is provided for producing mostly 5β,6β-epoxides of Δ^5-unsaturated steroids using certain ketones as the catalyst along with an oxidizing agent, or by using certain dioxiranes. In another aspect of the invention, a method is provided for producing mostly 5β,6β-epoxides of steroids from Δ^5-unsaturated steroids having a substituent at the 3α-position by an epoxidation reaction using a ketone along with an oxidizing agent under conditions effective to generate epoxides, or using a dioxirane under conditions effective to generate epoxides.

[0013] A whole range of Δ^5-unsaturated steroids, bearing different functional groups such as hydroxy, carbonyl, acetyl or ketal group, as well as different side chains, are converted to the corresponding synthetically and biologically interesting 5β,6β-epoxides with excellent β-selectivities and high yields.

BRIEF DESCRIPTION OF THE DRAWINGS

[0014] Fig. 1 is a diagrammatic representation of the general epoxidation reaction between Δ^5-unsaturated steroids and mCPBA or dioxirane;

[0015] Fig. 2 is a listing of chemical structures corresponding to ketones 1-4 and steroids 5-20;

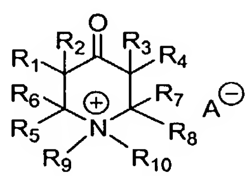
[0016] Fig. 3 is a diagrammatic representation of the epoxidation reaction of the present invention; and

[0017] Figs. 4 - 70 are ^{1}H NMR spectra of 5β,6β-epoxides of steroids and 5α,6α-epoxides of steroids including those epoxides of steroids synthesized as products by the method of the present invention and purified epoxides of steroids used as comparative control standards (referred to as "authentic samples").

DETAILED DESCRIPTION OF THE INVENTION

[0018] The present invention provides highly β-selective epoxidation of Δ^5-unsaturated steroids catalyzed by ketones or mediated by dioxiranes. More specifically, the present invention demonstrates that high β-selectivity can be achieved by increasing the steric size of either the α-substituents of dioxiranes or the 3α substituents of Δ^5-steroids. In some embodiments of the invention, the epoxidation reaction can provide said epoxides in at least about 5:1 β/α-epoxide ratio.

[0019] In one aspect of the invention, a method of producing mostly 5β,6β-epoxides of steroids from Δ^5-unsaturated steroids comprises an epoxidation reaction using a ketone and an oxidizing agent under conditions effective to generate epoxides, wherein the ketone is selected from compounds of generic formula I,



I

in which R_1 or R_4 in formula (I) is selected from alkyl, halogenated alkyl, aryl, OR (where R = H, alkyl or aryl), OCOR (where R = H, alkyl or aryl), OCOOR (where R = alkyl or aryl), $OCOOCH_2R$ (where R = aryl), $OCONR_1R_2$ (where R_1 or R_2 = H, alkyl or aryl), $OSiR_1R_2R_3$ (where R_1, R_2 or R_3 = alkyl or aryl), and halogen;

[0020] R_2 or R_3 in formula (I) is selected from H, alkyl, halogenated alkyl, aryl, OR (where R = H, alkyl or aryl), OCOR (where R = H, alkyl or aryl), OCOOR (where R = alkyl or aryl),

$OCOOCH_2R$ (where R = aryl), $OCONR_1R_2$ (where R_1 or R_2 = H, alkyl or aryl), $OSiR_1R_2R_3$ (where R_1, R_2 or R_3 = alkyl or aryl), and halogen;

[0021] R_5, R_6, R_7 or R_8 in formula (I) is selected from H, alkyl, halogenated alkyl, aryl, COOR (where R = H, alkyl or aryl), and $CONR_1R_2$ (where R_1 or R_2 = H, alkyl or aryl);

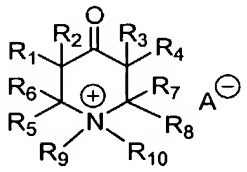
[0022] R_9 or R_{10} in formula (I) is selected from alkyl, halogenated alkyl, and aryl; and

[0023] A in formula (I) is selected from halogen, OTf, BF_4, OAc, NO_3, BPh_4, PF_6, and SbF_6.

[0024] In another aspect of the invention, a method of producing mostly 5β,6β-epoxides of steroids from Δ^5-unsaturated steroids having a substituent at the 3α-position comprises an epoxidation reaction using a ketone and an oxidizing agent under conditions effective to generate epoxides. The substituent at the 3α-position can be selected from OR (where R = H, alkyl or aryl), $O(CH_2)_nOR$ (where n = 1, 2 or 3, R = H, alkyl or aryl), $O(CH_2)_mSO_nR$ (where n = 1, 2 or 3; n = 0, 1 or 2; R = H, alkyl or aryl), $OSiR_1R_2R_3$ (where R_1, R_2 or R_3 = alkyl or aryl), OSO_nR (where n = 0, 1 or 2; R = H, alkyl or aryl), OCO_nR (where n = 1 or 2; R = H, alkyl or aryl), $OCONR_1R_2$ (where R_1 or R_2 = H, alkyl or aryl), OPO_nR (where where n = 2 or 3; R = alkyl or aryl), NR_1R_2 (where R_1 or R_2 = H, alkyl or aryl), $NR_1CO_nR_2$ (where n = 1 or 2; R_1 or R_2 = H, alkyl or aryl), $NR_1CONR_2R_3$ (where R_1, R_2 or R_3 = H, alkyl or aryl), $NR_1SO_nR_2$ (where n = 1 or 2; R_1 = H, alkyl or aryl, R_2 = alkyl or aryl), NPhth (Phth = phthaloyl group), $^+NR_1R_2R_3$ (where R_1, R_2, or R_3 = H, alkyl or aryl), $SiR_1R_2R_3$ (where R_1, R_2, or R_3 = H, alkyl or aryl), SO_nR (where n = 0, 1 or 2; R = H, alkyl or aryl), SCO_nR (where n = 1 or 2; R = H, alkyl or aryl), halogen, CN, NO_2, alkyl, aryl, COOR (where R = H, alkyl or aryl), and $CONR_1R_2$ (where R_1 or R_2 = H, alkyl or aryl).

[0025] Further in accordance with this aspect of the invention, the Δ^5-unsaturated steroid having a substituent at the 3α-position can be selected from the group consisting of Δ^5-unsaturated steroids having a ketal derivative of ketone group or a thioketal derivative of ketone group at the 3-position.

[0026] Further in accordance with this aspect of the invention, the ketone used in the epoxidation reaction can be selected from the group consisting of compounds of generic formula II, III, IV, and V wherein

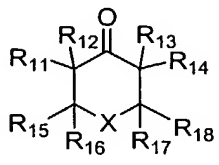


II

R_1, R_2, R_3, or R_4 in formula (II) is selected from H, alkyl, halogenated alkyl, aryl, OR (where R = H, alkyl or aryl), OCOR (where R = H, alkyl or aryl), OCOOR (where R = alkyl or aryl), $OCONR_1R_2$ (where R_1 or R_2 = H, alkyl or aryl), $OSiR_1R_2R_3$ (where R_1, R_2 or R_3 = alkyl or aryl), and halogen;

[0027] R_5, R_6, R_7, R_8, R_9 or R_{10} in formula (II) is selected from H, alkyl, halogenated alkyl, aryl, COOR (where R = H, alkyl or aryl), and $CONR_1R_2$ (where R_1 or R_2 = H, alkyl or aryl);

[0028] A in formula (II) is selected from halogen, OTf, BF_4, OAc, NO_3, BPh_4, PF_6, and SbF_6;

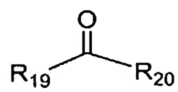


III

[0029] X in formula (III) is selected from $(CR_1R_2)_n$ (where n = 1, 2, 3, 4, or 5; R_1 or R_2 = H, alkyl or aryl), O, S, SO, SO_2, and NR (where R = H, alkyl or aryl);

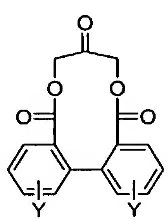
[0030] R_{11}, R_{12}, R_{13}, or R_{14} in formula (III) is selected from H, alkyl, halogenated alkyl, aryl, OR (where R = H, alkyl or aryl), OCOR (where R = H, alkyl or aryl), OCOOR (where R = alkyl or aryl), $OCONR_1R_2$ (where R_1 or R_2 = H, alkyl or aryl), $OSiR_1R_2R_3$ (where R_1, R_2 or R_3 = alkyl or aryl), and halogen;

[0031] R_{15}, R_{16}, R_{17}, or R_{18} in formula (III) is selected from H, alkyl, halogenated alkyl, aryl, COOR (where R = H, alkyl or aryl), and $CONR_1R_2$ (where R_1 or R_2 = H, alkyl or aryl);



IV

[0032] R_{19} or R_{20} in formula (IV) is selected from alkyl, halogenated alkyl, aryl, $CR_1R_2OCOR_3$ (where R_1, R_2 or R_3= H, alkyl or aryl), $CR_1R_2OCOOR_3$ (where R_1 or R_2 = H, alkyl or aryl; R_3 = alkyl or aryl), $CR_1R_2NR_3COOR_4$ (where R_1, R_2 or R_3 = H, alkyl or aryl, R_4 = alkyl or aryl), $CR_1R_2NR_3COR_4$ (where R_1, R_2, R_3 or R_4= H, alkyl or aryl), and $CR_1R_2NR_3SO_2R_4$ (where R_1, R_2 or R_3 = H, alkyl or aryl; R_4 = alkyl or aryl); and

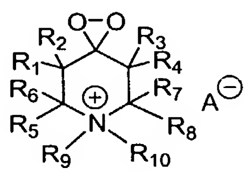


V

[0033] Y in formula (V) is selected from H, alkyl, halogenated alkyl, aryl, NO_2, CN, F, Cl, Br, I, COOR (where R = H or alkyl), OR (where R = H, alkyl or aryl), OSO_2R (where R = H, alkyl or aryl), OSOR (where R = H, alkyl or aryl), OSR (where R = H, alkyl or aryl), SO_2R (where R = H, alkyl or aryl), SO_3R (where R = H, alkyl or aryl), SOON R_1R_2 (where R_1 or R_2 = H, alkyl or aryl), NR_1SOOR_2 (where R_1 = H, alkyl or aryl; R_2 = alkyl or aryl), NR_1SOR_2 (where R_1 = H, alkyl or aryl; R_2 = alkyl or aryl), $CR_1R_2OR_3$ (where R_1, R_2 or R_3 = H, alkyl or aryl), $CR_1(OR_2)_2$

(where R_1= H or alkyl; R_2 = alkyl), CF_3, CF_2CF_3, OTf, OTs, OCOR (where R = H, alkyl or aryl), and $OSiR_1R_2R_3$ (where R_1, R_2 or R_3 = alkyl or aryl).

[0034] In yet another aspect of the invention, a method of producing mostly 5β,6β-epoxides of steroids from Δ^5-unsaturated steroids comprises an epoxidation reaction using a dioxirane under conditions effective to generate epoxides, wherein said dioxirane is selected from compounds of generic formula VI,



VI

[0035] R_1 or R_4 in formula (VI) is selected from alkyl, halogenated alkyl, aryl, OR (where R = H, alkyl or aryl), OCOR (where R = H, alkyl or aryl), OCOOR (where R = alkyl or aryl), $OCOOCH_2R$ (where R = aryl), $OCONR_1R_2$ (where R_1 or R_2 = H, alkyl or aryl), $OSiR_1R_2R_3$ (where R_1, R_2 or R_3 = alkyl or aryl), and halogen;

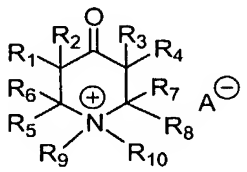
[0036] R_2 or R_3 in formula (VI) is selected from H, alkyl, halogenated alkyl, aryl, OR (where R = H, alkyl or aryl), OCOR (where R = H, alkyl or aryl), OCOOR (where R = alkyl or aryl), $OCOOCH_2R$ (where R = aryl), $OCONR_1R_2$ (where R_1 or R_2 = H, alkyl or aryl), $OSiR_1R_2R_3$ (where R_1, R_2 or R_3 = alkyl or aryl), and halogen;

[0037] R_5, R_6, R_7 or R_8 in formula (VI) is selected from H, alkyl, halogenated alkyl, aryl, COOR (where R = H, alkyl or aryl), and $CONR_1R_2$ (where R_1 or R_2 = H, alkyl or aryl);

[0038] R_9 or R_{10} in formula (VI) is selected from alkyl, halogenated alkyl, and aryl; and

[0039] A in formula (VI) is selected from halogen, OTf, BF_4, OAc, NO_3, BPh_4, PF_6, and SbF_6.

[0040] The dioxirane can be generated in situ from a ketone and an oxidizing agent selected from potassium peroxomonosulfate, sodium hypochlorite, sodium perborate, hydrogen peroxide, and peracids, wherein said ketone is selected from compounds of generic formula I,



I

[0041] R_1 or R_4 in formula (I) is selected from alkyl, halogenated alkyl, aryl, OR (where R = H, alkyl or aryl), OCOR (where R = H, alkyl or aryl), OCOOR (where R = alkyl or aryl), $OCOOCH_2R$ (where R = aryl), $OCONR_1R_2$ (where R_1 or R_2 = H, alkyl or aryl), $OSiR_1R_2R_3$ (where R_1, R_2 or R_3 = alkyl or aryl), and halogen;

[0042] R_2 or R_3 in formula (I) is selected from H, alkyl, halogenated alkyl, aryl, OR (where R = H, alkyl or aryl), OCOR (where R = H, alkyl or aryl), OCOOR (where R = alkyl or aryl), $OCOOCH_2R$ (where R = aryl), $OCONR_1R_2$ (where R_1 or R_2 = H, alkyl or aryl), $OSiR_1R_2R_3$ (where R_1, R_2 or R_3 = alkyl or aryl), and halogen;

[0043] R_5, R_6, R_7 or R_8 in formula (I) is selected from H, alkyl, halogenated alkyl, aryl, COOR (where R = H, alkyl or aryl), and $CONR_1R_2$ (where R_1 or R_2 = H, alkyl or aryl);

[0044] R_9 or R_{10} in formula (I) is selected from alkyl, halogenated alkyl, and aryl; and

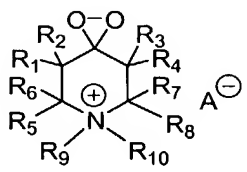
[0045] A in formula (I) is selected from halogen, OTf, BF_4, OAc, NO_3, BPh_4, PF_6, and SbF_6.

[0046] In yet another aspect of the invention, a method of producing mostly 5β,6β-epoxides of steroids from Δ^5-unsaturated steroids having a substituent at the 3α-position comprises an epoxidation reaction using a dioxirane under conditions effective to generate epoxides. In

accordance with this aspect of the invention, the substituent at the 3α-position can be selected from OR (where R = H, alkyl or aryl), $O(CH_2)_nOR$ (where n = 1, 2 or 3, R = H, alkyl or aryl), $O(CH_2)_mSO_nR$ (where n = 1, 2 or 3; n = 0, 1 or 2; R = H, alkyl or aryl), $OSiR_1R_2R_3$ (where R_1, R_2 or R_3 = alkyl or aryl), OSO_nR (where n = 0, 1 or 2; R = H, alkyl or aryl), OCO_nR (where n = 1 or 2; R = H, alkyl or aryl), $OCONR_1R_2$ (where R_1 or R_2 = H, alkyl or aryl), OPO_nR (where where n = 2 or 3; R = alkyl or aryl), NR_1R_2 (where R_1 or R_2 = H, alkyl or aryl), $NR_1CO_nR_2$ (where n = 1 or 2; R_1 or R_2 = H, alkyl or aryl), $NR_1CONR_2R_3$ (where R_1, R_2 or R_3 = H, alkyl or aryl), $NR_1SO_nR_2$ (where n = 1 or 2; R_1 = H, alkyl or aryl, R_2 = alkyl or aryl), NPhth (Phth = phthaloyl group), $^{+}NR_1R_2R_3$ (where R_1, R_2, or R_3 = H, alkyl or aryl), $SiR_1R_2R_3$ (where R_1, R_2, or R_3 = H, alkyl or aryl), SO_nR (where n = 0, 1 or 2; R = H, alkyl or aryl), SCO_nR (where n = 1 or 2; R = H, alkyl or aryl), halogen, CN, NO_2, alkyl, aryl, COOR (where R = H, alkyl or aryl), and $CONR_1R_2$ (where R_1 or R_2 = H, alkyl or aryl).

[0047] Further in accordance with this aspect of the invention, the Δ^5-unsaturated steroid having a substituent at the 3α-position can be selected from the group consisting of Δ^5-unsaturated steroids having a ketal derivative of a ketone group or a thioketal derivative of a ketone group at the 3-position.

[0048] Further in accordance with this aspect of the invention, the dioxirane can be selected from the group consisting of compounds of generic formula VII, VIII, IX and X.

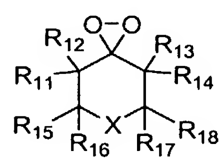


VII

[0049] R_1, R_2, R_3, or R_4 in formula (VII) is selected from H, alkyl, halogenated alkyl, aryl, OR (where R = H, alkyl or aryl), OCOR (where R = H, alkyl or aryl), OCOOR (where R = alkyl or aryl), $OCOOCH_2R$ (where R = aryl), $OCONR_1R_2$ (where R_1 or R_2 = H, alkyl or aryl), $OSiR_1R_2R_3$ (where R_1, R_2 or R_3 = alkyl or aryl), and halogen;

[0050] R_5, R_6, R_7, R_8, R_9 or R_{10}, in formula (VII) is selected from H, alkyl, halogenated alkyl, aryl, COOR (where R = H, alkyl or aryl), and $CONR_1R_2$ (where R_1 or R_2 = H, alkyl or aryl);

A in formula (VII) is selected from halogen, OTf, BF_4, OAc, NO_3, BPh_4, PF_6, and SbF_6;

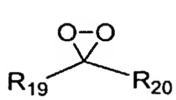


VIII

[0051] X in formula (VIII) is selected from $(CR_1R_2)_n$ (where n = 1, 2, 3, 4, or 5; R_1 or R_2 = H, alkyl or aryl), O, S, SO, SO_2, and NR (where R = H, alkyl or aryl);

[0052] R_{11}, R_{12}, R_{13}, or R_{14} in formula (VIII) is selected from H, alkyl, halogenated alkyl, aryl, OR (where R = H, alkyl or aryl), OCOR (where R = H, alkyl or aryl), OCOOR (where R = alkyl or aryl), $OCOOCH_2R$ (where R = aryl), $OCONR_1R_2$ (where R_1 or R_2 =H, alkyl or aryl), $OSiR_1R_2R_3$ (where R_1, R_2 or R_3 = alkyl or aryl), and halogen;

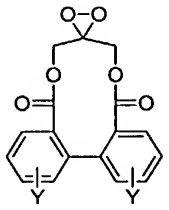
[0053] R_{15}, R_{16}, R_{17}, or R_{18} in formula (VIII) is selected from H, alkyl, halogenated alkyl, aryl, COOR (where R = H, alkyl or aryl), and $CONR_1R_2$ (where R_1 or R_2 = H, alkyl or aryl);



IX

[0054] R_{19} or R_{20} in formula (IX) is selected from alkyl, halogenated alkyl, aryl, $CR_1R_2OCOR_3$ (where R_1, R_2 or R_3= H, alkyl or aryl), $CR_1R_2OCOOR_3$ (where R_1 or R_2 = H, alkyl or aryl; R_3 =

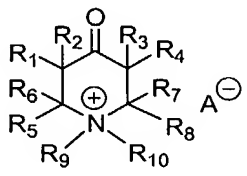
alkyl or aryl), $CR_1R_2NR_3COOR_4$ (where R_1, R_2 or R_3 = H, alkyl or aryl, R_4 = alkyl or aryl), $CR_1R_2NR_3COR_4$ (where R_1, R_2, R_3 or R_4 = H, alkyl or aryl), $CR_1R_2NR_3SO_2R_4$ (where R_1, R_2 or R_3 = H, alkyl or aryl; R_4 = alkyl or aryl); and



X

[0055] Y in formula (X) is selected from H, alkyl, halogenated alkyl, aryl, NO_2, CN, F, Cl, Br, I, COOR (where R = H or alkyl), OR (where R = H, alkyl or aryl), OSO_2R (where R = H, alkyl or aryl), OSOR (where R = H, alkyl or aryl), OSR (where R = H, alkyl or aryl), SO_2R (where R = H, alkyl or aryl), SO_3R (where R = H, alkyl or aryl), SOON R_1R_2 (where R_1 or R_2 = H, alkyl or aryl), NR_1SOOR_2 (where R_1 = H, alkyl or aryl; R_2 = alkyl or aryl), NR_1SOR_2 (where R_1 = H, alkyl or aryl; R_2 = alkyl or aryl), $CR_1R_2OR_3$ (where R_1, R_2 or R_3 = H, alkyl or aryl), $CR_1(OR_2)_2$ (where R_1 = H or alkyl; R_2 = alkyl), CF_3, CF_2CF_3, OTf, OTs, OCOR (where R = H, alkyl or aryl), and $OSiR_1R_2R_3$ (where R_1, R_2 or R_3 = alkyl or aryl).

[0056] The dioxirane can be generated in situ from a ketone and an oxidizing agent selected from potassium peroxomonosulfate, sodium hypochlorite, sodium perborate, hydrogen peroxide, and peracids. In such embodiments of the invention, the ketone can be selected from the group consisting of compounds of generic formula II, III, IV, and V,

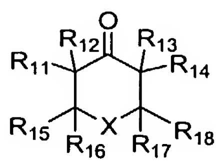


II

[0057] R_1, R_2, R_3, or R_4 in formula (II) is selected from H, alkyl, halogenated alkyl, aryl, OR (where R = H, alkyl or aryl), OCOR (where R = H, alkyl or aryl), OCOOR (where R = alkyl or aryl), $OCOOCH_2R$ (where R = aryl), $OCONR_1R_2$ (where R_1 or R_2 =H, alkyl or aryl), $OSiR_1R_2R_3$ (where R_1, R_2 or R_3 = alkyl or aryl), and halogen;

[0058] R_5, R_6, R_7, R_8, R_9 or R_{10} in formula (II) is selected from H, alkyl, halogenated alkyl, aryl, COOR (where R = H, alkyl or aryl), and $CONR_1R_2$ (where R_1 or R_2 = H, alkyl or aryl);

[0059] A in formula (II) is selected from halogen, OTf, BF_4, OAc, NO_3, BPh_4, PF_6, and SbF_6;

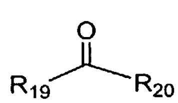


III

[0060] X in formula (III) is selected from $(CR_1R_2)_n$ (where n = 1, 2, 3, 4, or 5; R_1 or R_2 = H, alkyl or aryl), O, S, SO, SO_2, and NR (where R = H, alkyl or aryl);

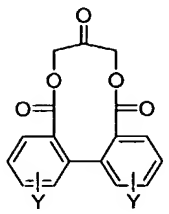
[0061] R_{11}, R_{12}, R_{13}, or R_{14} in formula (III) is selected from H, alkyl, halogenated alkyl, aryl, OR (where R = H, alkyl or aryl), OCOR (where R = H, alkyl or aryl), OCOOR (where R = alkyl or aryl), $OCOOCH_2R$ (where R = aryl), $OCONR_1R_2$ (where R_1 or R_2 =H, alkyl or aryl), $OSiR_1R_2R_3$ (where R_1, R_2 or R_3 = alkyl or aryl), and halogen;

[0062] R_{15}, R_{16}, R_{17}, or R_{18} in formula (III) is selected from H, alkyl, halogenated alkyl, aryl, COOR (where R = H, alkyl or aryl), and $CONR_1R_2$ (where R_1 or R_2 = H, alkyl or aryl);



IV

[0063] R_{19} or R_{20} in formula (IV) is selected from alkyl, halogenated alkyl, aryl, $CR_1R_2OCOR_3$ (where R_1, R_2 or R_3= H, alkyl or aryl), $CR_1R_2OCOOR_3$ (where R_1 or R_2 = H, alkyl or aryl; R_3 = alkyl or aryl), $CR_1R_2NR_3COOR_4$ (where R_1, R_2 or R_3 = H, alkyl or aryl, R_4 = alkyl or aryl), $CR_1R_2NR_3COR_4$ (where R_1, R_2, R_3 or R_4 = H, alkyl or aryl), $CR_1R_2NR_3SO_2R_4$ (where R_1, R_2 or R_3 = H, alkyl or aryl; R_4 = alkyl or aryl); and

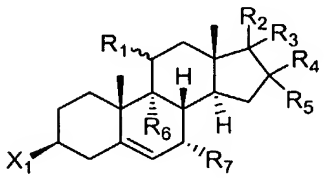


V

[0064] Y in formula (V) is selected from H, alkyl, halogenated alkyl, aryl, NO_2, CN, F, Cl, Br, I, COOR (where R = H or alkyl), OR (where R = H, alkyl or aryl), OSO_2R (where R = H, alkyl or aryl), OSOR (where R = H, alkyl or aryl), OSR (where R = H, alkyl or aryl), SO_2R (where R = H, alkyl or aryl), SO_3R (where R = H, alkyl or aryl), SOON R_1R_2 (where R_1 or R_2 = H, alkyl or aryl), NR_1SOOR_2 (where R_1 = H, alkyl or aryl; R_2 = alkyl or aryl), NR_1SOR_2 (where R_1 = H, alkyl or aryl; R_2 = alkyl or aryl), $CR_1R_2OR_3$ (where R_1, R_2 or R_3 = H, alkyl or aryl), $CR_1(OR_2)_2$ (where R_1 = H or alkyl; R_2 = alkyl), CF_3, CF_2CF_3, OTf, OTs, OCOR (where R = H, alkyl or aryl), and $OSiR_1R_2R_3$ (where R_1, R_2 or R_3 = alkyl or aryl).

[0065] Epoxidation reactions in accordance with the invention and using dioxiranes can be carried out in a solvent selected from acetonitrile, dimethoxymethane, acetone, dioxane, dimethoxyethane, tetrahydrofuran, dichloromethane, chloroform, benzene, toluene, diethylether, water and mixtures thereof.

[0066] In accordance with one embodiment of the invention herein, a method of producing mostly 5β,6β-epoxides of steroids comprises epoxidation reactions of Δ^5-unsaturated steroids of generic formula XI catalyzed by ketones of generic formula XII, wherein



XI

[0067] X_1 in formula (XI) is selected from H, OR (where R = H or alkyl), OCH_2OCH_3, OCOR (where R = alkyl or aryl), $OSiR_1'R_2'R_3'$ (where R_1', R_2' or R_3' = alkyl or aryl), halogen, CN, alkyl, aryl, and COOR (where R = H, alkyl or aryl);

[0068] R_1 in formula (XI) is selected from H, OR (where R = H or alkyl), OCOR (where R = alkyl or aryl), OCH_2OCH_3, halogen, CF_3, and CF_2CF_3;

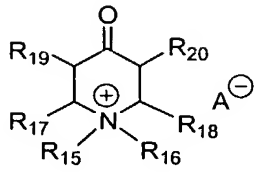
[0069] R_2 and R_3 in formula (XI) are each selected from the group consisting of H, alkyl, aryl, halogen, OR (where R = H or alkyl), OCOR (where R = alkyl or aryl), $OSiR_1'R_2'R_3'$ (where R_1', R_2' or R_3' = alkyl or aryl), COR (where R = alkyl), $COCH_2OR$ (where R = H or alkyl), $COCH_2OCOR$ (where R = alkyl or aryl), $COCH_2F$, COOR (where R = H or alkyl), $C(OCH_2CH_2O)R$ (where R = alkyl), $C(OCH_2CH_2O)CH_2OR$ (where R = H or alkyl), $C(OCH_2CH_2O)CH_2OCOR$ (where R = alkyl or aryl), and $C(OCH_2CH_2O)CH_2F$; or, are selected from the group consisting of O, OCH_2CH_2O, and $OCH_2CH_2CH_2O$;

[0070] R_4 in formula (XI) is selected from H, C_1–C_4 alkyl, halogen, OR (where R = H or alkyl), OCOR (where R = alkyl or aryl), and $OSiR_1'R_2'R_3'$ (where R_1', R_2' or R_3' = alkyl or aryl);

[0071] R_5 in formula (XI) is selected from H, C_1–C_4 alkyl, halogen, OR (where R = H or alkyl), OCOR (where R = alkyl or aryl), and $OSiR_1'R_2'R_3'$ (where R_1', R_2' or R_3' = alkyl or aryl);

[0072] R_6 in formula (XI) is selected from H, halogen, OR (where R = H or alkyl), and OCOR (where R = alkyl or aryl);

[0073] R_7 in formula (XI) is selected from H, halogen, OR (where R = H or alkyl), and OCOR (where R = alkyl or aryl);



XII

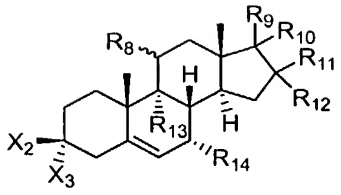
[0074] R_{15} and R_{16} in formula (XII) are each selected from alkyl and aryl;

[0075] R_{17} and R_{18} in formula (XII) are each selected from H, alkyl, aryl, COOR (where R = H, alkyl or aryl), and $CONR_1R_2$ (where R_1 or R_2 = H, alkyl or aryl);

[0076] R_{19} and R_{20} in formula (XII) are each selected from C_1–C_4 alkyl, halogenated alkyl, and halogen; and

[0077] A in formula (XII) is selected from OTf, BF_4, OAc, NO_3, BPh_4, PF_6, and SbF_6.

[0078] In another embodiment of the instant invention, a method of producing mostly 5β,6β-epoxides of steroids comprises epoxidation reactions of Δ^5-unsaturated steroids of generic formula XIII catalyzed by ketones of generic formula XIV, XV, XVI, and XVII, wherein



XIII

[0079] X_2 in formula (XIII) is selected from the group consisting of H, OR (where R = H or alkyl), OCH_2OCH_3, OCOR (where R = alkyl or aryl), $OSiR_1'R_2'R_3'$ (where R_1', R_2' or R_3' = alkyl or aryl), halogen, CN, alkyl, aryl, and COOR (where R = H, alkyl or aryl), and,

[0080] X_3 in formula (XIII) is selected from the group consisting of OR (where R = H or alkyl), OCH_2OCH_3, OCOR (where R = alkyl or aryl), $OSiR_1'R_2'R_3'$ (where R_1', R_2' or R_3' = alkyl or aryl), halogen, CN, NO_2, alkyl, and aryl; or,

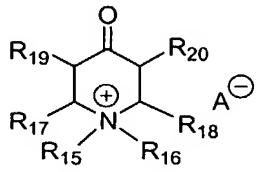
[0081] X_2 and X_3 in formula (XIII) are selected from the group consisting of O, OCH_2CH_2O, and $OCH_2CH_2CH_2O$;

[0082] R_8 in formula (XIII) is selected from H, OR (where R = H or alkyl), OCOR (where R = alkyl or aryl), OCH_2OCH_3, halogen, CF_3, and CF_2CF_3;

[0083] R_9 and R_{10} in formula (XIII) are each selected from the group consisting of H, alkyl, aryl, halogen, OR (where R = H or alkyl), OCOR (where R = alkyl or aryl), $OSiR_1'R_2'R_3'$ (where R_1', R_2' or R_3' = alkyl or aryl), COR (where R = alkyl), $COCH_2OR$ (where R = H or alkyl), $COCH_2OCOR$ (where R = alkyl or aryl), $COCH_2F$, COOR (where R = H or alkyl), $C(OCH_2CH_2O)R$ (where R = alkyl), $C(OCH_2CH_2O)CH_2OR$ (where R = H or alkyl), $C(OCH_2CH_2O)CH_2OCOR$ (where R = alkyl or aryl), and $C(OCH_2CH_2O)CH_2F$; or R_9 and R_{10} in formula (XIII) are selected from the group consisting of O, OCH_2CH_2O, and $OCH_2CH_2CH_2O$;

[0084] R_{11} and R_{12} in formula (XIII) are each selected from the group consisting of H, C_1–C_4 alkyl, halogen, OR (where R = H or alkyl), OCOR (where R = alkyl or aryl), and $OSiR_1'R_2'R_3'$ (where R_1', R_2' or R_3' = alkyl or aryl);

[0085] R_{13} and R_{14} in formula (XIII) are each selected from the group consisting of H, halogen, OR (where R = H or alkyl), and OCOR (where R = alkyl or aryl);



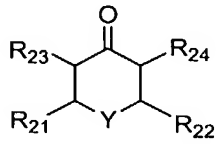
XIV

[0086] R_{15} or R_{16} in formula (XIV) is selected from alkyl and aryl;

[0087] R_{17} or R_{18} in formula (XIV) is selected from H, alkyl, aryl, COOR (where R = H, alkyl or aryl), and $CONR_1R_2$ (where R_1 or R_2 = H, alkyl or aryl);

[0088] R_{19} or R_{20} in formula (XIV) is selected from H, C_1–C_4 alkyl, halogenated alkyl, and halogen; and

[0089] A in formula (XIV) is selected from OTf, BF_4, OAc, NO_3, BPh_4, PF_6, and SbF_6;

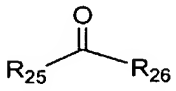


XV

[0090] Y in formula (XV) is selected from CH_2, O, S, SO, SO_2, and NR (where R = H or alkyl);

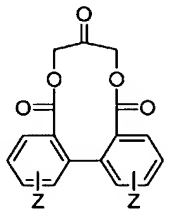
[0091] R_{21} or R_{22} in formula (XV) is selected from H, alkyl, aryl, COOR (where R = H, alkyl or aryl), and $CONR_1R_2$ (where R_1 or R_2 = H, alkyl or aryl);

[0092] R_{23} or R_{24} in formula (XV) is selected from H, halogen, C_1–C_4 alkyl, halogenated alkyl, and OCOR (where R = alkyl or aryl);



XVI

[0093] R_{25} or R_{26} in formula (XVI) is selected from C_1–C_4 alkyl, halogenated alkyl, CH_2OCOR (where R = alkyl or aryl); and



XVII

[0094] Z in formula (XVII) is selected from H, C_1–C_4 alkyl, aryl, NO_2, CN, F, Cl, Br, I, COOR (where R = alkyl), CH_2OR (where R = H or alkyl), $CH(OR)_2$ (where R = alkyl), CF_3, CF_2CF_3, OTf, OTs, OCOR (where R = alkyl or aryl), and $OSiR_1'R_2'R_3'$ (where R_1', R_2' or R_3' = alkyl or aryl).

[0095] In each of the disclosed embodiments, C_1–C_4 alkyl can be selected from the group consisting of methyl, ethyl, normal-propyl, iso-propyl, normal-butyl, iso-butyl, sec-butyl, and tert-butyl; and said aryl can be selected from the group consisting of phenyl, substituted phenyl, naphthyl, and substituted naphthyl groups. The epoxidation reactions can be carried out in a homogeneous solvent system selected from the group consisting of dimethoxymethane-acetonitrile-water, acetonitrile-water, acetone-water, dioxane-water, dimethoxyethane-water, and tetrahydrofuran-water, and mixtures thereof. Alternatively, the epoxidation reactions can be carried out in a biphasic solvent system selected from the group consisting of dichloromethane-

water, chloroform-water, benzene-water, toluene-water, dimethoxymethane-water, or diethylether-water and mixtures thereof.

[0096] Suitable oxidation agents for the epoxidation reactions of the instant invention include potassium peroxomonosulfate, sodium hypochlorite, sodium perborate, hydrogen peroxide, and peracids.

[0097] The epoxidation reactions of the instant invention catalyzed by a ketone can be carried out at a temperature within the range from about -10 °C to about 40 °C. Direct dioxirane epoxidation reactions of the instant invention can be carried out at a temperature within the range of from about -40°C to about 40°C. Some epoxidation reactions of the instant invention can be carried out at about room temperature.

[0098] The epoxidation reactions of the instant invention can be carried out at a pH within the range from about 7.0 to about 12.0. Some such epoxidation reactions can be carried out at a pH within the range from about 7.0 to about 7.5. The pH can be controlled by using a pH-stat machine such as is known in the art, or a buffer. Suitable buffers include solutions of sodium bicarbonate, sodium carbonate, sodium borate, sodium hydrogenphosphate, sodium dihydrogenphosphate, sodium hydroxide, potassium hydrogenphosphate, potassium dihydrogenphosphate, potassium bicarbonate, potassium carbonate and potassium hydroxide.

[0099] We first examined four efficient ketone catalysts **1–4** for the in situ epoxidation of cholesterol **5** (Fig. 2). A modified homogeneous solvent system (a mixture of DMM/CH_3CN/H_2O in a 3:1:2 ratio) was used to increase the solubility of steroid substrates (Fig. 3). The results are summarized in Table 1. The ratio of β/α-epoxides was determined by integration of C(6) proton signals in the ^1H NMR spectra of the crude residues (δ 3.00–3.15 ppm

for β-epoxides and δ 2.75–2.95 ppm for α-epoxides). While ketones **1–3** exhibited poor β-selectivities (β/α epoxide ratio *ca.* 1:1; entries 1–3), ketone **4** with the most bulky α-substituent gave the best β-selectivity (β/α epoxide ratio 15.1:1; entry 4). A variety of 3β-substituted Δ^5-steroids **6–10** (Fig. 2) were then subjected to the in situ epoxidation conditions with 20–30 mol % of ketone **4**. The results revealed that ketone **4** generally gave high β-selectivities (β/α epoxide ratio >8.5:1) and high yields (entries 4–10). It is interesting to note that Δ^5-steroids with a free C3-OH group were directly converted to their 5β,6β-epoxides with high selectivity and yields (entries 4, 5, and 7-9). (Note: The free 3-OH group of Δ^5-unsaturated steroids is not compatible with some metal-based oxidants in the epoxidation reactions.) Meanwhile, a wide range of functional groups such as hydroxyl, methoxyl, methoxymethyl ether, and carbonyl group were well tolerated under the mild and neutral reaction conditions (room temperature, pH 7–7.5).

[00100] Epoxidation reactions of 3α-substituted Δ^5-steroids **11–20** were also carried out with ketone catalysts **1–4** (Fig. 2) and the ketone catalyst acetone. For epicholesterol **11** with a 3*α*-OH group, the epoxidation reactions catalyzed by ketones **1** and **4** gave much higher *β*-selectivities than those by ketones **2** and **3** (Table 2; entries 1–4) and acetone (see Table 3). This is because ketones **1** and **4** have larger α-substituents. For substrates with 3*α*-substituents larger than the OH group (**12–20**), the in situ epoxidation catalyzed by ketones **1–4** and acetone produced almost single 5*β*,6*β*-isomers (Table 2, β/α ratio >49:1, entries 5–24; Table 3). Substrates with 3-ketal group are of particular interest since highly α-selective epoxidation with trifluoroperacetic acid has been reported for this class of Δ^5-steroids. Epoxidation of substrates **13–20** with *m*CPBA gave *ca.* 1:1 ratio of β/α-epoxides. The epoxidation reactions catalyzed by ketone **2**

were highly efficient as only 5 mol% of the catalyst was needed even on a preparative scale. For example, a multi-gram scale (10 mmol) epoxidation of substrate **18** catalyzed by ketone **2** (5 mol %) provided almost a single β-epoxide (β/α-epoxide ratio > 99:1) in 88 % yield. These results clearly demonstrate the power of ketone-catalyzed epoxidation method.

[00101] In summary, we have developed a general, efficient and environmentally friendly method for highly β-selective epoxidation of Δ^5-unsaturated steroids. With this method in hand, a library of 5*β*,6*β*-epoxides and their derivatives can be readily constructed and then screened for potential ligands that bind to orphan nuclear receptors. This is crucial for elucidating the biological functions of those receptors as well as for drug discovery.

General Experimental

[00102] The ^1H and ^{13}C NMR spectra (Figs. 4-70) were recorded in deuteriochloroform ($CDCl_3$) with tetramethylsilane (TMS) as internal standard at ambient temperature on a Bruker Avance DPX 300 or 500 Fourier Transform Spectrometer. Infrared absorption spectra were recorded as a solution in CH_2Cl_2 on a Bio-Rad FTS 165 Fourier Transform Spectrophotometer. Mass spectra were recorded with a Finningan MAT 95 mass spectrometer for both low resolution and high resolution mass spectra.

[00103] Substrates **5**, **6**, **8**, **9**, ketone **1**, tetrahydrothiopyran-4-one (precursor of ketone 2), and Oxone® were purchased from Aldrich or Acros Chemical Co. and used without further purification. Substrates **7**, **10**, **11**, **12**, **13–20**, and ketones **3**, **4** were prepared according to the literature procedures.

Typical Procedure for in situ Epoxidation Reactions

[00104] **Epoxidation of Cholesterol 5 Catalyzed by Ketone 4 (Table 1, Entry 4).** To a solution of cholesterol **5** (116 mg 0.3 mmol) and ketone **4** (41 mg, 0.09 mmol) in dimethoxymethane (DMM, 9 mL) and acetonitrile (CH_3CN, 3 mL) at room temperature was added an aqueous Na_2•EDTA solution (6 mL, 4×10^{-4} M). To this mixture was added in portions a mixture of Oxone® (922 mg, 1.5 mmol) and sodium bicarbonate (391 mg, 4.65 mmol) over the reaction period. The reaction mixture was poured into water, and extracted with ethyl acetate three times. The combined organic layers were dried over anhydrous $MgSO_4$ and filtered through a pad of silica gel. The ratio of α/β-epoxides was determined by ^1H NMR analysis of the crude residue which was obtained after removal of the solvent under reduced pressure. Pure products were obtained after flash column chromatography on silica gel (99 mg, 82% yield).

[00105] **Epoxidation of Substrate 13 Catalyzed by Ketone 2 (Table 2, Entry 8).** To a solution of substrate **13** (112 mg 0.3 mmol) and tetrahydrothiopyran-4-one (1.7 mg, 0.015 mmol) in dimethoxymethane (DMM, 9 mL) and acetonitrile (CH_3CN, 3 mL) at room temperature was added an aqueous Na_2•EDTA solution (6 mL, 4×10^{-4} M). To this mixture was added in portions a mixture of Oxone® (922 mg, 1.5 mmol) and sodium bicarbonate (391 mg, 4.65 mmol) over a period of 1.5 h. The reaction was complete in 2 h as shown by TLC. The reaction mixture was poured into water, and extracted with ethyl acetate three times. The combined organic layers were dried over anhydrous $MgSO_4$ and filtered through a pad of silica gel. The ratio of α/β-epoxides was determined by ^1H NMR analysis of the crude residue which was obtained after removal of the solvent under reduced pressure. Pure epoxide was obtained after flash column chromatography on silica gel (110 mg, 94% yield).

Procedure for Preparative Scale Epoxidation Reactions

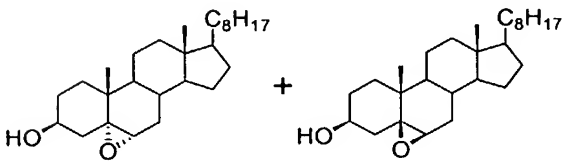
[00106] **Epoxidation of Substrate 9 Catalyzed by Ketone 4 (Table 1, Entry 9).** To a solution of substrate **9** (3.17 g 10 mmol) and ketone **4** (1.37g, 3 mmol) in dimethoxymethane (DMM, 300 mL) and acetonitrile (CH_3CN, 100 mL) at room temperature was added an aqueous Na_2•EDTA solution (200 mL, 4×10^{-4} M). To this mixture was added in portions a mixture of Oxone® (30.74 g, 50 mmol) and sodium bicarbonate (13.02 g, 155 mmol) over a period of 8 h. The reaction was complete in 10 h as shown by TLC. The reaction mixture was poured into water, and extracted with ethyl acetate three times. The combined organic layers were dried over anhydrous $MgSO_4$ and filtered through a pad of silica gel. The ratio of α/β-epoxides was determined by ^{1}H NMR analysis of the crude residue which was obtained after removal of the solvent under reduced pressure. Pure products were obtained after flash column chromatography on silica gel (2.86 g, 86% yield).

[00107] **Epoxidation of Substrate 18 Catalyzed by Ketone 2 (Table 2, Entry 19).** To a solution of substrate **18** (4.03 g 10 mmol) and tetrahydrothiopyran-4-one (58 mg, 0.5 mmol) in dimethoxymethane (DMM, 300 mL) and acetonitrile (CH_3CN, 100 mL) at room temperature was added an aqueous Na_2•EDTA solution (200 mL, 4×10^{-4} M). To this mixture was added in portions a mixture of Oxone® (30.74 mg, 50 mmol) and sodium bicarbonate (13.02 g, 155 mmol) over a period of 4 h. The reaction was complete in 5 h as shown by TLC. The reaction mixture was poured into water, and extracted with ethyl acetate three times. The combined organic layers were dried over anhydrous $MgSO_4$ and filtered through a pad of silica gel. The ratio of α/β-epoxides was determined by ^{1}H NMR analysis of the crude residue which was obtained after removal of the solvent under reduced pressure. Pure epoxide was obtained after flash column chromatography on silica gel (3.68 g, 88% yield).

General Procedure for Epoxidation of Δ^5-Unsaturated Steroids with *m*CPBA

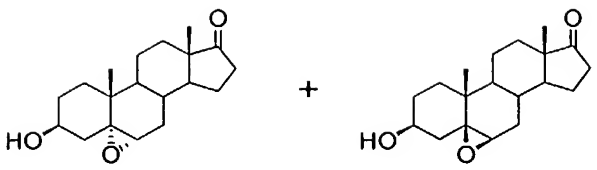
[00108] Sodium bicarbonate (0.4 mmol) and *m*CPBA (0.2 mmol) were added to a solution of substrate (0.1 mmol) in CH_2Cl_2 (3 ml). The resulting mixture was stirred at room temperature for 2 h and quenched with a solution of saturated aqueous $Na_2S_2O_3$. The reaction mixture was diluted with ethyl acetate and washed with a solution of saturated aqueous $NaHCO_3$ and brine. The organic layer was dried over anhydrous $MgSO_4$ and filtered through a pad of silica gel. The product analysis was performed as above.

Characterization Data for Epoxides



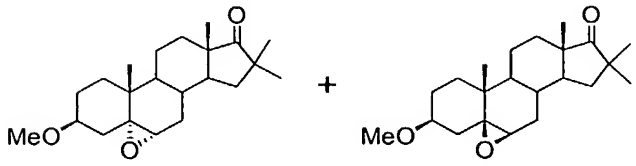
[00109] **5a** and **5b** (as a mixture of 1:15.1 ratio; Table 1, Entry 4):

[00110] ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.94–3.86 (m, 1/16.1 × 1H, 3α-H), 3.74–3.64 (m, 15.1/16.1 × 1H, 3α-H), 3.06 (d, J = 2.2 Hz, 15.1/16.1 × 1H, 6α-H), 2.90 (d, J = 4.3 Hz, 1/16.1 × 1H, 6β-H), 1.06 (s, 1/16.1 × 3H, 19-CH_3), 0.99 (s, 15.1/16.1 × 3H, 19-CH_3), 0.89 (d, J = 6.6 Hz, 15.1/16.1 × 3H, 21-CH_3), 0.86 (d, J = 6.6 Hz, 15.1/16.1 × 6H, 26-CH_3 and 27-CH_3), 0.64 (s, 15.1/16.1 × 3H, 18-CH_3), 0.61 (s, 1/16.1 × 3H, 18-CH_3); ^{13}C NMR of **5b** (75.5 MHz, $CDCl_3$) δ 69.32, 63.76, 63.04, 56.21, 56.20, 51.32, 42.27, 42.18, 39.82, 39.48, 37.22, 36.12, 35.71, 34.84, 32.59, 30.97, 29.76, 28.14, 27.99, 24.18, 23.80, 22.81, 22.55, 21.98, 18.66, 17.05, 11.75.



[00111] 6a and 6b (as a mixture of 1:10.4 ratio; Table 1, Entry 5):

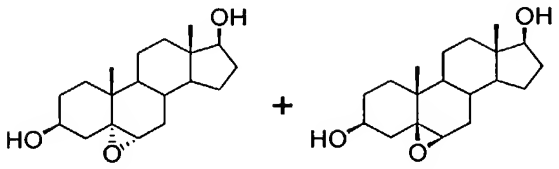
[00112] ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.95–3.85 (m, 1/11.4 × 1H, 3α-H), 3.76–3.65 (m, 10.4/11.4 × 1H, 3α-H), 3.13 (d, J = 2.5 Hz, 10.4/11.4 × 1H, 6α-H), 2.95 (d, J = 4.3 Hz, 1/11.4 × 1H, 6β-H), 1.09 (s, 1/11.4 × 3H, 19-CH_3), 1.03 (s, 10.4/11.4 × 3H, 19-CH_3), 0.85 (s, 10.4/11.4 × 3H, 18-CH_3) 0.82 (s, 1/11.4 × 3H, 18-CH_3); ^{13}C NMR of **6b** (75.5 MHz, $CDCl_3$) δ 220.97, 69.21, 63.32, 63.05, 51.47, 51.18, 47.49, 42.05, 37.24, 35.74, 35.10, 31.51, 31.46, 30.93, 29.47, 21.73, 21.28, 17.08, 13.47.



[00113] 7a and 7b (as a mixture of 1:9; Table 1, Entry 6):

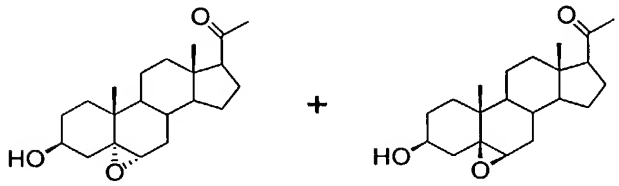
[00114] ^{1}H NMR (500 MHz, $CDCl_3$) δ = 3.45–3.38 (m, 1/10 × 1H, 3α-H), 3.34 (s, 3H, OCH_3), 3.28–3.22 (m, 9/10 × 1H, 3α-H), 3.11 (d, J = 2.4 Hz, 9/10 × 1H, 6α-H), 2.95 (d, J = 4.4 Hz, 1/10 × 1H, 6β-H), 1.18 (s, 9/10 × 3H, 19-CH_3), 1.17 (s, 1/10 × 3H, 19-CH_3), 1.02 (s, 9/10 × 6H, 20-CH_3 and 21-CH_3), 0.87 (s, 9/10 × 3H, 18-CH_3), 0.85 (s, 1/10 × 3H, 18-CH_3); ^{13}C NMR of **9b** (75.5 MHz, $CDCl_3$) δ = 225.00, 77.70, 63.15, 63.04, 55.71, 51.37, 48.52, 48.01, 45.15, 38.63, 37.82, 36.75, 35.54, 32.30, 31.66, 28.93, 27.27, 27.02, 25.95, 21.08, 17.13, 14.08; IR (CH_2Cl_2) 1730 cm^{-1}; LRMS (EI, 20 eV) *m/z* 346 (100), 314 (15), 123 (31), 108 (22); HRMS (EI, 20 eV)

calcd for $C_{22}H_{34}O_3$ (M^+): 346.2508, found: 346.2508; Anal. Calcd for $C_{22}H_{34}O_3$: C, 76.26; H, 9.89; Found: C, 76.14; H, 9.90.



[00115] 8a and 8b (as a mixture of 1:8.8 ratio; Table 1, Entry 7):

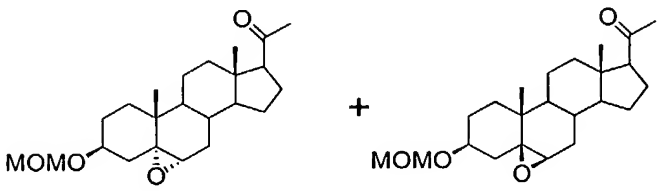
[00116] ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.95–3.84 (m, 1/9.8 × 1H, 3α-H), 3.74–3.64 (m, 8.8/9.8 × 1H, 3α-H), 3.60 (t, J = 8.5 Hz, 1H, 17α-H), 3.07 (d, J = 2.4 Hz, 8.8/9.8 × 1H, 6α-H), 2.91 (d, J = 4.4 Hz, 1/9.8 × 1H, 6β-H), 1.07 (s, 1/9.8 × 3H, 19-CH_3), 1.01 (s, 8.8/9.8 × 3H, 19-CH_3), 0.72 (s, 8.8/9.8 × 3H, 18-CH_3), 0.69 (s, 1/9.8 × 3H, 18-CH_3); ^{13}C NMR of **8b** (75.5 MHz, $CDCl_3$) δ 81.81, 69.31, 63.51, 63.01, 51.48, 50.74, 42.67, 42.15, 37.25, 36.62, 34.99, 32.19, 30.97, 30.42, 29.81, 23.31, 21.60, 17.12, 10.86.



[00117] 9a and 9b (as a mixture of 1:11.6; Table 1, Entry 8):

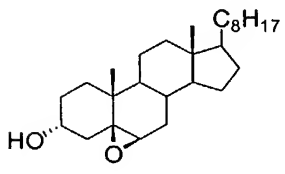
[00118] ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.94–3.87 (m, 1/12.6 × 1H, 3α-H), 3.75–3.65 (m, 11.6/12.6 × 1H, 3α-H), 3.08 (d, J = 2.3 Hz, 11.6/12.6 × 1H, 6α-H), 2.92 (d, J = 4.4 Hz, 1/12.6 × 1H, 6β-H), 2.11 (s, 11.6/12.6 × 3H, 21-CH_3) 1.06 (s, 1/12.6 × 3H, 19-CH_3), 1.00 (s, 11.6/12.6 × 3H, 19-CH_3), 0.59 (s, 11.6/12.6 × 3H, 18-CH_3) 0.56 (s, 1/12.6 × 3H, 18-CH_3); ^{13}C NMR of **9b**

(75.5 MHz, $CDCl_3$) δ 209.48, 69.29, 63.67, 63.50, 62.89, 56.33, 51.19, 43.89, 42.12, 38.84, 37.25, 34.92, 32.51, 31.46, 30.97, 29.76, 24.36, 22.77, 21.96, 17.07, 13.11.



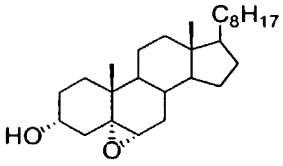
[00119] **10a** and **10b** (as a mixture of 1:8.5; Table 1, Entry 10):

[00120] ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.73–4.64 (m, 2H, OCH_2O), 3.83–3.74 (m, 1/9.5 × 1H, 3α-H), 3.65–3.55 (m, 8.5/9.5 × 1H, 3α-H), 3.36 (s, 8.5/9.5 × 3H, OCH_3), 3.35 (s, 1/9.5 × 3H, OCH_3), 3.08 (d, J = 2.3 Hz, 8.5/9.5 × 1H, 6α-H), 2.91 (d, J = 4.3 Hz, 1/9.5 × 1H, 6β-H), 2.11 (s, 8.5/9.5 × 3H, 21-CH_3), 1.06 (s, 1/9.5 × 3H, 19-CH_3), 1.00 (s, 8.5/9.5 × 3H, 19-CH_3), 0.60 (s, 8.5/9.5 × 3H, 18-CH_3), 0.56 (s, 1/9.5 × 3H, 18-CH_3); ^{13}C NMR of **11b** (75.5 MHz, $CDCl_3$) δ 209.35, 94.67, 74.18, 63.67, 63.44, 62.82, 56.33, 55.26, 51.08, 43.88, 39.43, 38.84, 37.07, 35.16, 32.48, 31.45, 29.74, 28.13, 24.35, 22.77, 21.94, 17.07, 13.11; IR (CH_2Cl_2) 1700 cm^{-1}; EIMS (20 eV) *m/z* 376 (100), 314 (90), 133 (36), 95 (33); HRMS (EI, 20 eV) calcd for $C_{23}H_{36}O_4$ (M^+): 376.2614, found: 376.2617; Anal. Calcd for $C_{23}H_{36}O_4$: C, 73.37; H, 9.64; Found: C, 73.11; H, 9.68.



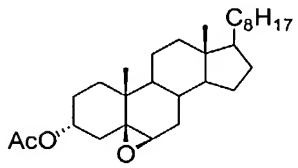
[00121] 11b:

[00122] ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.19 (br s, 1H, 3β-H), 3.07 (d, J = 2.0 Hz, 1H, 6α-H), 0.97 (s, 3H, 19-CH_3), 0.89 (d, J =6.6 Hz, 3H, 21-CH_3), 0.86 (d, J =6.6 Hz, 6H, 26-CH_3 and 27-CH_3), 0.64 (s, 3H, 18-CH_3); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 67.03, 63.70, 61.97, 56.31, 56.20, 50.38, 42.31, 39.87, 39.86, 39.49, 36.14, 35.74, 35.53, 33.19, 32.37, 29.82, 28.40, 28.17, 27.99, 24.18, 23.83, 22.81, 22.55, 21.69, 18.67, 17.00, 11.78.



[00123] 11a:

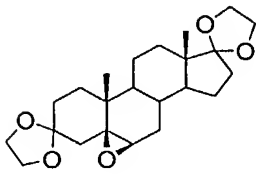
[00124] ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.10–4.07 (m, 1H, 3β-H), 2.87 (d, J = 4.5 Hz, 1H, 6β-H), 1.04 (s, 3H, 19-CH_3), 0.89 (d, J =6.6 Hz, 3H, 21-CH_3), 0.86 (d, J =6.6 Hz, 6H, 26-CH_3 and 27-CH_3), 0.61 (s, 3H, 18-CH_3); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 67.98, 65.43, 57.79, 56.86, 55.84, 42.66, 42.32, 39.49, 39.36, 36.41, 36.13, 35.76, 35.52, 29.62, 28.92, 28.63, 28.59, 28.07, 28.00, 24.02, 23.84, 22.82, 22.56, 20.28, 18.64, 15.34, 11.86.



[00125] 12b:

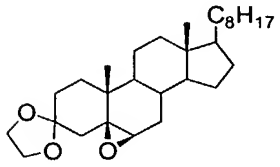
[00126] ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.12–5.10 (m, 1H, 3β-H), 3.00 (d, J = 2.0 Hz, 1H, 6α-H), 2.04 (s, 3H, CH_3COO), 0.99 (s, 3H, 19-CH_3), 0.89 (d, J = 6.6 Hz, 3H, 21-CH_3), 0.86 (d, J = 6.6 Hz, 6H, 26-CH_3 and 27-CH_3), 0.65 (s, 3H, 18-CH_3); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 170.52,

70.50, 63.28, 61.69, 56.33, 56.27, 50.20, 42.34, 39.86, 39.49, 36.63, 36.15, 35.76, 35.43, 33.78, 32.43, 29.81, 28.19, 28.01, 25.47, 24.19, 23.85, 22.82, 22.56, 21.71, 21.34, 18.68, 17.13, 11.78.



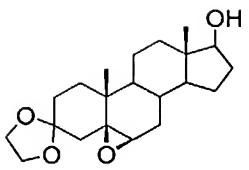
[00127] 13b:

[00128] ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.97–3.79 (m, 8H, OCH_2CH_2O), 3.06 (d, J = 2.1 Hz, 1H, 6α-H), 1.00 (s, 3H, 19-CH_3), 0.82 (s, 3H, 18-CH_3); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 119.12, 109.19, 64.97, 64.33, 64.12, 63.94, 62.90, 62.76, 49.81, 49.53, 45.50, 41.29, 35.43, 34.97, 33.91, 31.44, 30.64, 30.38, 29.78, 22.44, 21.20, 16.94, 13.96.



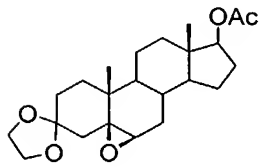
[00129] 14b:

^{1}H NMR (300 MHz, $CDCl_3$) δ 3.97–3.85 (m, 4H, OCH_2CH_2O), 3.05 (d, J = 1.9 Hz, 1H, 6α-H), 0.99 (s, 3H, 19-CH_3), 0.89 (d, J = 6.7 Hz, 3H, 21-CH_3), 0.86 (d, J = 6.6 Hz, 6H, 26-CH_3 and 27-CH_3), 0.64 (s, 3H, 18-CH_3); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 109.45, 64.27, 64.09, 63.29, 62.96, 56.24, 56.15, 49.85, 42.28, 41.46, 39.81, 39.47, 36.11, 35.71, 35.61, 35.01, 32.27, 30.82, 29.67, 28.15, 27.98, 24.16, 23.79, 22.81, 22.54, 21.89, 18.66, 17.06, 11.75.



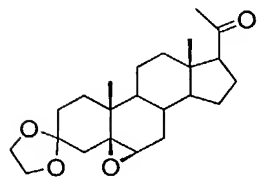
[00130] 15b:

[00131] ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.97–3.87 (m, 4H, OCH_2CH_2O), 3.60 (t, J = 8.5 Hz, 1H, 17α-H), 3.07 (d, J = 2.2 Hz, 1H, 6α-H), 1.01 (s, 3H, 19-CH_3), 0.72 (s, 3H, 18-CH_3); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 109.41, 81.78, 64.31, 64.14, 63.14, 63.05, 50.79, 50.07, 42.70, 41.45, 36.62, 35.66, 35.17, 31.87, 30.81, 30.45, 29.73, 23.31, 21.53, 17.14, 10.88.



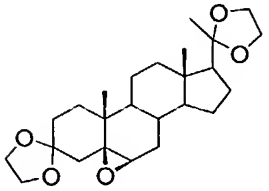
[00132] 16b:

[00133] ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.56 (dd, J = 9.0, 7.9 Hz, 1H, 17α-H), 3.95–3.89 (m, 4H, OCH_2CH_2O), 3.07 (d, J = 2.2 Hz, 1H, 6α-H), 2.03 (s, 3H, CH_3COO), 1.00 (s, 3H, 19-CH_3), 0.77 (s, 3H, 18-CH_3); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 171.20, 109.34, 82.64, 64.30, 64.14, 63.09, 63.00, 50.53, 49.94, 42.33, 41.45, 36.79, 35.68, 35.14, 31.85, 30.78, 29.52, 27.43, 23.44, 21.39, 21.16, 17.11, 11.84.



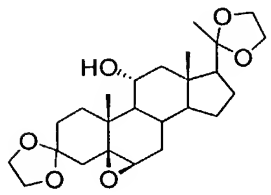
[00134] 17b:

[00135] ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.95–3.90 (m, 4H, OCH_2CH_2O), 3.07 (d, J = 2.1 Hz, 1H, 6α-H), 2.11 (s, 3H, 21-CH_3), 1.00 (s, 3H, 19-CH_3), 0.60 (s, 3H, 18-CH_3); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 209.41, 109.37, 64.33, 64.16, 63.66, 63.15, 62.95, 56.40, 49.84, 43.92, 41.42, 38.85, 35.71, 35.10, 32.21, 31.47, 30.82, 29.70, 24.36, 22.78, 21.90, 17.09, 13.12.



[00136] 18b:

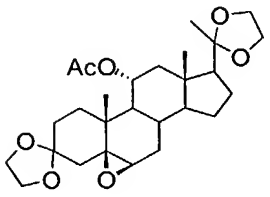
[00137] ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.04–3.81 (m, 8H, OCH_2CH_2O), 3.06 (d, J = 1.8 Hz, 1H, 6α-H), 1.28 (s, 3H, 21-CH_3), 1.00 (s, 3H, 19-CH_3), 0.74 (s, 3H, 18-CH_3); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 111.85, 109.44, 65.16, 64.29, 64.12, 63.26, 63.19, 63.00, 58.21, 56.12, 49.87, 41.75, 41.46, 39.44, 35.62, 35.06, 32.18, 30.82, 29.22, 24.54, 23.70, 22.90, 21.67, 17.10, 12.76.



[00138] 19b:

[00139] ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.03–3.81 (m, 9H, 11β-H and OCH_2CH_2O), 3.08 (d, J = 2.6 Hz, 1H, 6α-H), 1.28 (s, 3H, 21-CH_3), 1.20 (s, 3H, 19-CH_3), 0.76 (s, 3H, 18-CH_3); ^{13}C NMR

(75.5 MHz, $CDCl_3$) δ 111.47, 109.02, 68.68, 64.98, 64.17, 64.04, 63.35, 63.10, 62.90, 57.80, 57.01, 55.22, 50.60, 42.45, 41.81, 37.41, 35.87, 31.40, 30.57, 27.91, 24.40, 23.42, 22.97, 15.55, 13.86.



[00140] 20b:

[00141] ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.07 (td, J = 10.9, 4.8 Hz, 1H, 11β-H), 3.99–3.83 (m, 8H, OCH_2CH_2O), 3.08 (d, J = 2.7 Hz, 1H, 6α-H), 2.01 (s, 3H, CH_3COO), 1.24 (s, 3H, 21-CH_3), 1.02 (s, 3H, 19-CH_3), 0.82 (s, 3H, 18-CH_3); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 169.76, 111.42, 108.87, 72.38, 64.96, 64.28, 64.17, 63.16, 63.02, 62.69, 57.73, 55.09, 53.57, 45.36, 42.23, 41.86, 37.02, 35.85, 31.56, 30.70, 28.09, 24.46, 23.52, 23.19, 21.87, 16.06, 13.58.

Determination of the Ratio of β/α-epoxides

[00142] The ratio of β/α-epoxides was determined by integration of the C(6) proton signals in the ^{1}H NMR spetra (300 or 500 MHz) of crude residues (δ 3.00–3.15 ppm for β-epoxides and δ 2.75–2.95 ppm for α-epoxides). The authentic samples of **5a/5b–20a/20b** were prepared by epoxidation of substrates **5–20** with *m*CPBA according to the literature procedure.

EXAMPLES

Example 1: 5β,6β-Epoxycholestan-3β-ol (Catalyzed by Ketone **4**)

[00143] To a solution of cholesterol (116 mg 0.3 mmol) and ketone **4** (41 mg, 0.09 mmol) in dimethoxymethane (9 mL) and acetonitrile (3 mL) at room temperature was added an aqueous Na_2•EDTA solution (6 mL, 4×10^{-4} M). To this mixture was added in portions a mixture of Oxone® (922 mg, 1.5 mmol) and sodium bicarbonate (391 mg, 4.65 mmol) over the reaction period. The reaction mixture was poured into water, and extracted with ethyl acetate three times. The combined organic layers were dried over anhydrous $MgSO_4$ and filtered through a pad of silica gel. ^{1}H NMR analysis of the product showed that the ratio of β/α-epoxides was 15.1:1. Pure products were obtained after flash column chromatography on silica gel (99 mg, 82% yield).

Example 2: 5β,6β-Epoxyandrostene-3,17-dione 3,17-diethylene ketal (Catalyzed by ketone **1**)

[00144] To a solution of 5-androstene-3,17-dione 3,17-diethylene ketal (112 mg 0.3 mmol) in dimethoxymethane (9 mL) and acetonitrile (3 mL) was added an aqueous Na_2•EDTA solution (6 mL, 4×10^{-4} M), the resulting solution was cooled to 0–1 °C, followed by addition of 1,1,1-trifluoroacetone (0.54 mL, 6 mmol). To this solution was added in portions a mixture of Oxone® (922 mg, 1.5 mmol) and sodium bicarbonate (391 mg, 4.65 mmol) over a period of 0.5 h. The reaction was complete in 1 h as shown by TLC. The reaction mixture was poured into water, and extracted with ethyl acetate three times. The combined organic layers were dried over anhydrous $MgSO_4$ and filtered through a pad of silica gel. ^{1}H NMR analysis of the crude residue showed that the ratio of β/α-epoxides was >99:1. 5β,6β-Epoxyandrostene-3,17-dione 3,17-

diethylene ketal was obtained after flash column chromatography on silica gel (101 mg, 86% yield).

Example 3: 5β,6β-Epoxyandrostene-3,17-dione 3,17-diethylene ketal (Catalyzed by ketone **2**)

[00145] To a solution of 5-androstene-3,17-dione 3,17-diethylene ketal (112 mg 0.3 mmol) and tetrahydrothiopyran-4-one (1.7 mg, 0.015 mmol) in dimethoxymethane (9 mL) and acetonitrile (3 mL) at room temperature was added an aqueous Na_2•EDTA solution (6 mL, 4×10^{-4} M). To this mixture was added in portions a mixture of Oxone® (922 mg, 1.5 mmol) and sodium bicarbonate (391 mg, 4.65 mmol) over a period of 1.5 h. The reaction was complete in 2 h as shown by TLC. The reaction mixture was poured into water, and extracted with ethyl acetate three times. The combined organic layers were dried over anhydrous $MgSO_4$ and filtered through a pad of silica gel. ^{1}H NMR analysis of the crude residue showed that the ratio of β/α-epoxides was 96:1. 5β,6β-Epoxyandrostene-3,17-dione 3,17-diethylene ketal was obtained after flash column chromatography on silica gel (110 mg, 94% yield).

Example 4: 5β,6β-Epoxyandrostene-3,17-dione 3,17-diethylene ketal (Catalyzed by ketone **3**)

[00146] To a solution of 5-androstene-3,17-dione 3,17-diethylene ketal (112 mg 0.3 mmol) and ketone **3** (9 mg, 0.03 mmol) in dimethoxymethane (9 mL) and acetonitrile (3 mL) at room temperature was added an aqueous Na_2•EDTA solution (6 mL, 4×10^{-4} M). To this mixture was added in portions a mixture of Oxone® (922 mg, 1.5 mmol) and sodium bicarbonate (391 mg, 4.65 mmol) over a period of 1 h. The reaction was complete in 1.5 h as shown by TLC. The reaction mixture was poured into water, and extracted with ethyl acetate three times. The

combined organic layers were dried over anhydrous $MgSO_4$ and filtered through a pad of silica gel. ^1H NMR analysis of the crude residue showed that the ratio of β/α-epoxides was 49:1. 5β,6β-Epoxyandrostene-3,17-dione 3,17-diethylene ketal was obtained after flash column chromatography on silica gel (109 mg, 93% yield).

Example 5: 5β,6β-Epoxyandrostene-3,17-dione 3,17-diethylene ketal (Catalyzed by acetone)

[00147] To a solution of 5-androstene-3,17-dione 3,17-diethylene ketal (112 mg 0.3 mmol) and acetone (522 mg, 9 mmol) in dimethoxymethane (9 mL) and acetonitrile (3 mL) at room temperature was added an aqueous Na_2•EDTA solution (6 mL, 4×10^{-4} M). To this mixture was added in portions a mixture of Oxone® (922 mg, 1.5 mmol) and sodium bicarbonate (391 mg, 4.65 mmol) over a period of 4 h. The reaction was complete in 5 h as shown by TLC. The reaction mixture was poured into water, and extracted with ethyl acetate three times. The combined organic layers were dried over anhydrous $MgSO_4$ and filtered through a pad of silica gel. ^1H NMR analysis of the crude residue showed that the ratio of β/α-epoxides was >99:1. 5β,6β-Epoxyandrostene-3,17-dione 3,17-diethylene ketal was obtained after flash column chromatography on silica gel (110 mg, 94% yield).

Example 6: 5β,6β-Epoxyandrostene-3,17-dione 3,17-diethylene ketal (Acetone as catalyst and cosolvent)

[00148] To a solution of 5-androstene-3,17-dione 3,17-diethylene ketal (112 mg 0.3 mmol) in actone (15 mL) at room temperature was added an aqueous Na_2•EDTA solution (5 mL, 4×10^{-4} M). To this mixture was added in portions a mixture of Oxone® (922 mg, 1.5 mmol) and sodium bicarbonate (391 mg, 4.65 mmol) over a period of 1.5 h. The reaction was complete in 2

h as shown by TLC. The reaction mixture was poured into water, and extracted with ethyl acetate three times. The combined organic layers were dried over anhydrous $MgSO_4$ and filtered through a pad of silica gel. ^1H NMR analysis of the crude residue showed that the ratio of β/α-epoxides was >99:1. 5β,6β-Epoxyandrostene-3,17-dione 3,17-diethylene ketal was obtained after flash column chromatography on silica gel (105 mg, 90% yield).

Example 7: 5β,6β-Epoxy-3β-Hydroxypregnan-20-one (Catalyzed by ketone **4**)

[00149] To a solution of pregnenolone (3.17 g 10 mmol) and ketone **4** (1.37g, 3 mmol) in dimethoxymethane (300 mL) and acetonitrile (100 mL) at room temperature was added an aqueous Na_2•EDTA solution (200 mL, 4×10^{-4} M). To this mixture was added in portions a mixture of Oxone® (30.74 g, 50 mmol) and sodium bicarbonate (13.02 g, 155 mmol) over a period of 8 h. The reaction was complete in 10 h as shown by TLC. The reaction mixture was poured into water, and extracted with ethyl acetate three times. The combined organic layers were dried over anhydrous $MgSO_4$ and filtered through a pad of silica gel. ^1H NMR analysis of the product showed that he ratio of β/α-epoxides was 16.0:1. Pure products were obtained after flash column chromatography on silica gel (2.86 g, 86% yield).

Example 8: 5β,6β-Epoxy-11α-hydroxypregnene-3,20-dione 3-diethylene ketal (Catalyzed by ketone **2**)

[00150] To a solution of 5-pregnene-3,20-dione 3,20-diethylene ketal (4.03 g 10 mmol) and tetrahydrothiopyran-4-one (58 mg, 0.5 mmol) in dimethoxymethane (300 mL) and acetonitrile (100 mL) at room temperature was added an aqueous Na_2•EDTA solution (200 mL, 4×10^{-4} M). To this mixture was added in portions a mixture of Oxone® (30.74 mg, 50 mmol) and sodium bicarbonate (13.02 g, 155 mmol) over a period of 4 h. The reaction was complete in 5 h as

shown by TLC. The reaction mixture was poured into water, and extracted with ethyl acetate three times. The combined organic layers were dried over anhydrous $MgSO_4$ and filtered through a pad of silica gel. ^1H NMR analysis of the crude residue showed that the ratio of β/α-epoxides was >99:1. 5β,6β-Epoxypregnene-3,20-dione 3,20-diethylene ketal was obtained after flash column chromatography on silica gel (3.68 g, 88% yield).

Example 9: 5β,6β-Epoxy-3β-hydroxyandrostan-17-one (Catalyzed by ketone **4**)

[00151] Following the procedure of Example 1 above, dehydroisoandrosterone was epoxidized to 5β,6β-epoxy-3β-hydroxyandrostan-17-one.

Example 10: 5β,6β-Epoxy-16,16-dimethyl-3β-methoxyandrostan-17-one (Catalyzed by ketone **4**)

[00152] Following the procedure of Example 1 above, 16,16-dimethyl-3β-methoxy-5-androsten-17-one was epoxidized to 5β,6β-epoxy-16,16-dimethyl-3β-methoxyandrostan-17-one.

Example 11: 5β,6β-Epoxyandrostane-3β,17β-diol (Catalyzed by ketone **4**)

[00153] Following the procedure of Example 1 above, 5-androstene-3β,17β-diol was epoxidized to 5β,6β-epoxyandrostane-3β,17β-diol.

Example 12: 5β,6β-Epoxy-3β-methoxymethoxypregnan-20-one (Catalyzed by ketone **4**)

[00154] Following the procedure of Example 1 above, 3β-methoxymethoxy-5-pregnen-20-one was epoxidized to 5β,6β-epoxy-3β-methoxymethoxypregnan-20-one.

Example 13: 5β,6β-Epoxycholestan-3α-ol (Catalyzed by ketone **4**)

[00155] Following the procedure of Example 1 above, epicholesterol was epoxidized to 5β,6β-epoxycholestan-3α-ol.

Example 14: 5β,6β-Epoxy-3α-acetoxycholestane (Catalyzed by ketone **2**)

[00156] Following the procedure of Example 3 above, 3α-acetoxycholest-5-ene was epoxidized to 5β,6β-epoxy-3α-acetoxycholestane.

Example 15: 5β,6β-Epoxy-3α-acetoxycholestane (Catalyzed by ketone **4**)

[00157] Following the procedure of Example 1 above, 3α-acetoxycholest-5-ene was epoxidized to 5β,6β-epoxy-3α-acetoxycholestane.

Example 16: 5β,6β-Epoxycholestane-3-one 3-ethylene ketal (Catalyzed by ketone **2**)

[00158] Following the procedure of Example 3 above, 5-cholestene-3-one 3-ethylene ketal was epoxidized to 5β,6β-epoxycholestane-3-one 3-ethylene ketal.

Example 17: 5β,6β-Epoxycholestane-3-one 3-ethylene ketal (Catalyzed by ketone **4**)

[00159] Following the procedure of Example 1 above, 5-cholestene-3-one 3-ethylene ketal was epoxidized to 5β,6β-epoxycholestane-3-one 3-ethylene ketal.

Example 18: 5β,6β-Epoxy-17β-hydroxyandrostan-3-one 3-ethylene ketal (Catalyzed by ketone **2**)

[00160] Following the procedure of Example 3 above, 17β-hydroxyandrost-5-en-3-one 3-ethylene ketal was epoxidized to 5β,6β-epoxy-17β-hydroxyandrostan-3-one 3-ethylene ketal.

Example 19: 5β,6β-Epoxy-17β-hydroxyandrostan-3-one 3-ethylene ketal (Catalyzed by ketone **4**)

[00161] Following the procedure of Example 1 above, 17β-hydroxyandrost-5-en-3-one 3-ethylene ketal was epoxidized to 5β,6β-epoxy-17β-hydroxyandrostan-3-one 3-ethylene ketal.

Example 20: 5β,6β-Epoxy-17β-acetoxyandrostan-3-one 3-ethylene ketal (Catalyzed by ketone **2**)

[00162] Following the procedure of Example 3 above, 17β-acetoxyandrost-5-en-3-one 3-ethylene ketal was epoxidized to 5β,6β-epoxy-17β-acetoxyandrostan-3-one 3-ethylene ketal.

Example 21: 5β,6β-Epoxy-17β-acetoxyandrostan-3-one 3-ethylene ketal (Catalyzed by ketone **4**)

[00163] Following the procedure of Example 1 above, 17β-acetoxyandrost-5-en-3-one 3-ethylene ketal was epoxidized to 5β,6β-epoxy-17β-acetoxyandrostan-3-one 3-ethylene ketal.

Example 22: 5β,6β-Epoxypregnene-3,20-dione 3,20-diethylene ketal (Catalyzed by ketone **2**)

[00164] Following the procedure of Example 3 above, 5-pregnene-3,20-dione 3,20-diethylene ketal was epoxidized to 5β,6β-epoxypregnene-3,20-dione 3,20-diethylene ketal.

Example 23: 5β,6β-Epoxypregnene-3,20-dione 3,20-diethylene ketal (Catalyzed by ketone **4**)

[00165] Following the procedure of Example 1 above, 5-pregnene-3,20-dione 3,20-diethylene ketal was epoxidized to 5β,6β-epoxypregnene-3,20-dione 3,20-diethylene ketal.

Example 24: 5β,6β-Epoxypregnene-3,20-dione 3-diethylene ketal (Catalyzed by ketone **2**)

[redacted]

[00166] Following the procedure of Example 3 above, 5-pregnene-3,20-dione 3-ethylene ketal was epoxidized to 5β,6β-epoxypregnene-3,20-dione 3-ethylene ketal.

Example 25: 5β,6β-Epoxypregnene-3,20-dione 3-diethylene ketal (Catalyzed by ketone 4)

[00167] Following the procedure of Example 1 above, 5-pregnene-3,20-dione 3-ethylene ketal was epoxidized to 5β,6β-epoxypregnene-3,20-dione 3-ethylene ketal.

Example 26: 5β,6β-Epoxy-11α-hydroxypregnene-3,20-dione 3-diethylene ketal (Catalyzed by ketone 2)

[00168] Following the procedure of Example 3 above, 11α- hydroxy-5-pregnene-3,20-dione 3-ethylene ketal was epoxidized to 5β,6β-epoxy-11α-hydroxypregnene-3,20-dione 3-diethylene ketal.

Example 27: 5β,6β-Epoxy-11α-hydroxypregnene-3,20-dione 3-diethylene ketal (Catalyzed by ketone 4)

[00169] Following the procedure of Example 1 above, 11α- hydroxy-5-pregnene-3,20-dione 3-ethylene ketal was epoxidzed to 5β,6β-epoxy-11α-hydroxypregnene-3,20-dione 3-diethylene ketal.

Example 28: 5β,6β-Epoxy-11α-acetoxypregnene-3,20-dione 3-diethylene ketal (Catalyzed by ketone 2)

[00170] Following the procedure of Example 3 above, 11α- acetoxy-5-pregnene-3,20-dione 3-ethylene ketal was epoxidized to 5β,6β-epoxy-11α-acetoxypregnene-3,20-dione 3-diethylene ketal.

Example 29: 5β,6β-Epoxy-11α-acetoxypregnene-3,20-dione 3-diethylene ketal (Catalyzed by ketone **4**)

[00171] Following the procedure of Example 1 above, 11α- acetoxy-5-pregnene-3,20-dione 3-ethylene ketal was epoxidized to 5β,6β-epoxy-11α-acetoxypregnene-3,20-dione 3-diethylene ketal.

Example 30: 5β,6β-Epoxycholestan-3α-ol (catalyzed by ketone **1**)

[00172] Following the procedure of Example 2 above, epi-cholesterol was epoxidized to 5β,6β-epoxycholestan-3α-ol.

Example 31: 5β,6β-Epoxyandrostene-3,17-dione 3,17-diethylene ketal (catalyzed by ketone **4**)

[00173] Following the procedure of Example 1 above 5-cholestene-3-one 3-ethylene ketal was epoxidized to 5β,6β-epoxyandrostene-3,17-dione 3,17-diethylene ketal.

Example 32: 5β,6β-Epoxycholestane-3-one 3-ethylene ketal (catalyzed by acetone)

[00174] Following the procedure of Example 5 above, 5-cholestene-3-one 3-ethylene ketal was epoxidized to 5β,6β-epoxycholestane-3-one 3-ethylene ketal.

Example 33: 5β,6β-Epoxy-17β-acetoxyandrostan-3-one 3-ethylene ketal (catalyzed by acetone)

[00175] Following the procedure of Example 5 above, 17β-acetoxyandrost-5-en-3-one 3-ethylene ketal was epoxidized to 5β,6β-epoxy-17β-acetoxyandrostan-3-one 3-ethylene ketal.

Example 34: 5β,6β-Epoxypregnene-3,20-dione 3-ethylene ketal (catalyzed by ketone **2**)

[00176] Following the procedure of Example 3 above, 5-pregnene-3,20-dione 3-ethylene ketal was epoxidized to 5β,6β-epoxypregnene-3,20-dione 3-ethylene ketal.

Example 35: 5β,6β-Epoxypregnene-3,20-dione 3-ethylene ketal (catalyzed by ketone **4**)

[00177] Following the procedure of Example 1 above, 5-pregnene-3,20-dione 3-ethylene ketal was epoxidized to 5β,6β-epoxypregnene-3,20-dione 3-ethylene ketal.

Example 36: 5β,6β-Epoxypregnene-3,20-dione 3,20-diethylene ketal (catalyzed by acetone)

[00178] Following the procedure of Example 5 above, 5-pregnene-3,20-dione 3,20-diethylene ketal was epoxidized to 5β,6β-epoxypregnene-3,20-dione 3,20-diethylene ketal.

Example 37: 5β,6β-Epoxy-11α-hyrdoxypregnene-3,20-dione 3,20-diethylene ketal (catalyzed by acetone)

[00179] Following the procedure of Example 5 above, 11α-hyrdoxy-5-pregnene-3,20-dione 3,20-diethylene ketal was epoxidized to 5β,6β-epoxy-11α-hyrdoxypregnene-3,20-dione 3,20-diethylene ketal.

Example 38: 5β,6β-Epoxy-11α-hyrdoxypregnene-3,20-dione 3,20-diethylene ketal (catalyzed by ketone **2**)

[00180] Following the procedure of Example 3 above, 11α-hyrdoxy-5-pregnene-3,20-dione 3,20-diethylene ketal was epoxidized to 5β,6β-epoxy-11α-hyrdoxypregnene-3,20-dione 3,20-diethylene ketal.

Example 39: 5β,6β-Epoxy-11α-hyrdoxypregnene-3,20-dione 3,20-diethylene ketal (catalyzed by ketone **4**)

[00181] Following the procedure of Example 1 above, 11α-hyrdoxy-5-pregnene-3,20-dione 3,20-diethylene ketal was epoxidized to 5β,6β-epoxy-11α-hyrdoxypregnene-3,20-dione 3,20-diethylene ketal.

Example 40: 5β,6β-Epoxy-11α-acetoxypregnene-3,20-dione 3,20-diethylene ketal (catalyzed by ketone **2**)

[00182] Following the procedure of Example 3 above, 11α-acetoxy-5-pregnene-3,20-dione 3,20-diethylene ketal was epoxidized to 5β,6β-epoxy-11α-acetoxypregnene-3,20-dione 3,20-diethylene ketal.

Example 41: 5β,6β-Epoxy-11α-acetoxypregnene-3,20-dione 3,20-diethylene ketal (catalyzed by ketone **4**)

[00183] Following the procedure of Example 1 above, 11α-acetoxy-5-pregnene-3,20-dione 3,20-diethylene ketal was epoxidized to 5β,6β-epoxy-11α-acetoxypregnene-3,20-dione 3,20-diethylene ketal.

[00184] The invention has been described with reference to preferred embodiments. Those skilled in the art will perceive improvements, changes and modifications. Such improvements, changes and modifications are intended to be within the scope of the claims.

TABLE 1

Stereoselective epoxidation of 3β-substituted Δ^5-steroids by dioxiranes generated in situ.[a]

entry	ketone catalyst	substrate	catalyst loading (equivalent)	reaction time (h)[b]	yield (%)[c]	β/α-epoxide ratio[d,e]
1	**1**[f]	**5**	20	1.5	91	1/1.1 (1/4.0)
2	**2**	**5**	0.05	1.5	93	1.1/1
3	**3**	**5**	0.1	3	92	1/1.1
4	**4**	**5**	0.3	16	82	15.1/1
5	**4**	**6**	0.2	9	91	10.4/1 (1/3.9)
6	**4**	**7**	0.2	20	88	9.0/1 (1/3.1)
7	**4**	**8**	0.2	16	85	8.8/1 (1/3.1)
8	**4**	**9**	0.2	9	93	11.6/1 (1/4.3)
9[g]	**4**	**9**	0.3	10	86	16.0/1
10	**4**	**10**	0.2	20	83	8.5/1 (1/3.7)

[a] Unless otherwise indicated, reaction conditions were as follows: room temperature, 0.3 mmol of substrate, indicated amount of ketone, 1.5 mmol of Oxone®, 4.65 mmol of $NaHCO_3$, 9 mL of dimethoxymethane (DMM), 3 mL of CH_3CN, and 6 mL of aqueous Na_2•EDTA solution (4×10^{-4} M). [b] Time for complete epoxidation as shown by TLC. [c] Isolated yield. [d] The ratio of β/α-epoxides was determined by ^{1}H NMR spectroscopy (500 or 300 MHz). [e] The value in parentheses was the ratio of β/α-epoxides obtained with *m*CPBA as the oxidant. [f] The epoxidation reaction was carried out at 0–1 °C. [g] On a 10 mmol scale.

Note: An additional experiment was performed using ketone **4** and substrate **9** in which the catalyst loading and reaction time were 0.2 and 12 h, respectively. The subsequent epoxidation reaction resulted in an 89 % yield and a β/α-epoxide ratio of 11.4/1.

TABLE 2

Stereoselective epoxidation of 3α-substituted Δ^5-steroids by dioxiranes generated in situ[a]

entry	ketone	substrate	catalyst loading (equivalent)	reaction time (h)[b]	yield (%)[c]	β/α-epoxide ratio[d,e]
1	**1**[f]	**11**	20	2	90	19:1
2	**2**	**11**	0.05	2	93	5:1
3	**3**	**11**	0.1	3.5	91	4:1
4	**4**	**11**	0.2	8	92	90:1
5	**2**	**12**	0.05	4	82	72:1 (2:1)
6	**4**	**12**	0.3	18	84[g]	>99:1
7	**1**[e]	**13**	20	1	86	>99:1
8	**2**	**13**	0.05	2	94	96:1
9	**3**	**13**	0.1	1.5	93	49:1
10	**4**	**13**	0.3	12	84	>99:1
11	**2**	**14**	0.05	3.5	95	>99:1
12	**4**	**14**	0.3	18	86[h]	>99:1
13	**2**	**15**	0.05	2	88	79:1 (1:1)
14	**4**	**15**	0.2	10	83	86:1
15	**2**	**16**	0.05	3	95	91:1
16	**4**	**16**	0.2	12	82	>99:1
17	**2**	**17**	0.05	1	91	84:1 (1:1)
18	**4**	**17**	0.2	15	81	66:1
19	**2**	**18**	0.05	3.5	96	92:1
20	**4**	**18**	0.2	12	84	61:1
21	**2**	**19**	0.05	2	92	51:1
22	**4**	**19**	0.2	9	91	50:1
23	**2**	**20**	0.05	2	92	85:1 (1:1)
24	**4**	**20**	0.3	12	82	62:1

[a] Unless otherwise indicated, reaction conditions were as follows: room temperature, 0.3 mmol of substrate, indicated amount of ketone, 1.5 mmol of Oxone®, 4.65 mmol of $NaHCO_3$, 9 mL of dimethoxymethane (DMM), 3 mL of CH_3CN, and 6 mL of aqueous Na_2•EDTA solution (4×10^{-4} M). [b] Time for complete epoxidation as shown by TLC. [c] Isolated yield unless otherwise noted. [d] The ratio of β/α-epoxides was determined by ^1H NMR spectroscopy (500 or 300 MHz). [e] The value in parentheses was the ratio of β/α-epoxides obtained with *m*CPBA as the oxidant. [f] The epoxidation reaction was carried out at 0–1 °C. [g] Based on recovered starting material (82 % conversion). [h] Based on recovered starting material (61 % conversion).

TABLE 3

Stereoselective epoxidation of 3α-substituted Δ^5-steroids catalyzed by acetone.

Entry	substrate	catalyst loading (equivalent)	reaction time (h)[b]	yield (%)[c]	β/α-epoxide ratio[d,e]
1	**11**	20	5	90	3:1 (1:9.5)
2	**13**	20	5	94	>99:1[f] (1:1)
3	**14**	20	6	93	>99:1 (1:1)
4	**16**	20	3.5	93	>99:1 (1:1)
5	**18**	20	6	92	>99:1 (1:1)
6	**19**	20	5	91	43:1 (1:1)

[a] Unless otherwise indicated, reaction conditions were as follows: room temperature, 0.3 mmol of substrate, indicated amount of ketone, 1.5 mmol of Oxone®, 4.65 mmol of $NaHCO_3$, 9 mL of dimethoxymethane (DMM), 3 mL of CH_3CN, and 6 mL of aqueous Na_2•EDTA solution (4×10^{-4} M). [b] Time for complete epoxidation as shown by TLC. [c] Isolated yield. [d] The ratio of β/α-epoxides was determined by ^1H NMR spectroscopy (500 or 300 MHz). [e] The value in parentheses was the ratio of β/α-epoxides obtained with *m*CPBA as the oxidant. [f] In another run, the ratio of β/α-epoxides was > 99:1 with acetone and water (3:1) as solvents.